REMARKS

Specification

The Specification has been amended to update the status of the parent applications, as requested by the Examiner. The Specification has also been amended to correct a reference to Table 2 in lieu of Supplemental Table 1. No new matter has been added.

Rejection of Claims under 35 U.S.C. 112, first paragraph

The Examiner rejected Claims 3-5, 7, 8, 9 and 12-14, stating that it is not possible extrapolate the teachings in the specification to the enablement of the claims because it is "clear that the uptake of the Mab 833/drug is nonspecific for lung tissue itself." The Examiner also questioned how long it would take the agent of interest to destroy the lung and kill the recipient. Applicant respectfully asserts that this is a mischaracterization of the nature of the Mab 833 and its ability to target a specific tissue and to deliver a compound to that tissue.

The endothelium is a single layer of thin, flattened cells that form the blood vessel wall and separates the circulating blood (including cells and molecules) and from the underlying cells inside the tissue and constituting the tissue/organ. In most organs, the endothelium acts as a significant barrier to the free passage of blood-borne molecules and cells to the underlying interstitium and tissue cells (e.g., myocardial cells of the heart tissue cells). The endothelium itself is not a tissue, but an important cellular component forming a critical compartment of the tissue of the organ. As described in the Specification, monoclonal antibody 833 reacted with the surface of microvascular endothelium in lung tissue, as assessed by both immunoblotting and tissue immunostaining. A tissue test of lung, heart, brain, liver, kidney, adrenal, testes, intestine, skeletal muscle, and spleen, both Western blotting of whole tissue lysates and subcellular fractions, and immunohistochemical staining of fixed tissue sections, indicated lung specificity, as the antibody reacted with the endothelium only in lung tissue and did not stain the pulmonary artery (indicating specificity for microvasculature over larger blood vessels). The lung epithelial cells, especially obvious in the bronchi, were also nonreactive. The specificity of 833 Mab for the lung vasculature was also quite apparent when the antibody was injected into the tail vein of the rats. Mab 833 also had very low blood counts (> 10-fold less than the control) and very

significant tissue uptake in the lung (>50-fold over the control). It was quickly cleared or extracted from the blood by its specific binding to, and transport across, the endothelium of the blood vessel of the lung and not other tissues/organs. Most importantly, mAb 833 appeared specifically to accumulate most rapidly and significantly in the lung with very little detection in other organs. Mass balance analysis showed that a mean of 75±6.4% (833; ranging from 67 to 87%) of the injected dose (10 μg), is targeted to the lung tissue in just 30 minutes.

Mab 833 was found not only to be tissue-specific in its ability to target only lung endothelium, but also caveolae-specific: immunogold EM carried out on ultrathin frozen lung tissue sections showed that Mab 833 associated predominantly with the bulb and neck of the caveolae in microvascular endothelium, and not clathrin-coated pits or epithelial cells (including their caveolae). Larger blood vessel endothelium and controls using heart tissue or nonspecific mouse IgG_1 were negative. Thus, Mab 833 specifically recognizes an antigen that is expressed selectively in caveolae of microvascular endothelium of lung but not other tissues.

The data concerning the conjugate of the drug, dgRA, with the antibody, was presented as a demonstration that the antibody is capable of specifically delivering a drug to a particular tissue. The drug was delivered across the endothelium and only to the underlying cells within the lung tissue; it was not delivered across endothelium to any other organ system. This data clearly demonstrates tissue specificity. It also reveals the caveolae specificity of the antibody as well as specific penetration into the lung tissue (but not into other organs) from its specific ability to target the endothelial caveolae of the lung and not other organs.

The Examiner additionally states that "although Applicant's invention has clearly addressed the first problem [a need to develop antibodies that target a specific vasculature], the second problem, that is of tumor specificity, has not been addressed" (Office Action, p. 8). Applicant's Attorney notes that the broadest claims are not drawn to targeting a tumor specifically. The claims are drawn to delivering an agent of interest into and/or across a luminal surface of vascular endothelium in a tissue-specific manner, by selecting an agent of interest that binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface, wherein the component to which the agent binds and localizes is tissue specific; and contacting the luminal surface of vasculature with the agent of interest, thereby delivering the agent into and/or across the luminal surface of the

vascular endothelium in a tissue-specific manner. Applicant has clearly demonstrated identification and use of an antibody to deliver an agent into and across a luminal surface of vascular endothelium in a tissue-specific manner for lung tissue.

The Examiner additionally stated that the method was "clearly drawn to *in vivo* therapy of malignant tissue" (Office Action, page 9). However, as indicated above, the methods need not be limited to treatment of malignancies. The methods could also be used to deliver agents for treatment of other diseases of the lung (e.g., asthma, emphysema, tuberculosis, pneumonia, COPH, pulmonary hypertension, cystic fibrosis, and other acquired or genetic lung-related conditions). One of ordinary skill in the art, given the teachings of the specification regarding the use of Mab 833 to deliver an agent of interest specifically to lung tissue, would be able to identify agents that could similarly be delivered for the treatment of a wide variety of conditions.

The Examiner additionally rejected Claims 3-5, 7, 8, 9, and 12-14 under 35 U.S.C. 112, first paragraph, stating that "one cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that the identification of Mab 833... was a hoped for but unexpected event." Applicant's Attorney respectfully disagrees with the assertion that the teachings of the Specification cannot be so extrapolated. The identification of Mab 833 exemplifies the methods that one of ordinary skill in the art can utilize to identify other tissue-specific antibodies. One of ordinary skill in the art, given the teachings of the specification, would understand that the important characteristic of an antibody for use in the methods is that it binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface. The specification details how to test antibodies for such specificity. While a certain amount of experimentation may be necessary to identify an antibody having this desired characteristic, there is sufficient evidence in the Specification to guide one of ordinary skill in the art as to how to identify such an antibody. The test for enablement is not solely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976).

The Examiner additionally stated that it could not be predicted whether the epitope to which Mab 833 binds was evolutionarily conserved so that one of ordinary skill in the art would not be able to predict whether the use of the antibody would function in other species. Given the teachings of the Specification, however, one of ordinary skill in the art, using no more than routine experimentation such as the experimentation described in the Specification, would be able to utilize lung tissue samples from other species and easily determine whether Mab 833 similarly functioned in other species. Furthermore, one of ordinary skill in the art could use the teachings of the specification regarding the making and identification of Mab 833, to make and identify antibodies having similar tissue specificity in other species. Moreover, the Mab 833 can also be used by one of ordinary skill in the art to isolate the rat protein, to which homologues can quickly be identified in genomic databases and yield equivalent proteins for antibody generation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands*, 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985). A need for experimentation does not render the claimed invention unpatentable under 35 U.S.C. 112, first paragraph.

The Examiner also rejected Claims 3-5, 7, 8, 9 and 12-14 under 35 U.S.C. 112, first paragraph, stating that it did not appear that Applicant had possession of the broadly claimed invention "encompassing unidentified agents of interest that bind to unspecified antigens in unspecified caveolae in unspecified tissues" (Office Action, paragraph bridging pages 14-15).

Applicant's Specification provides a significant amount of description regarding the making and identification of a representative agent of interest that binds to and localizes to a component of caveolae of the luminal surface of the vascular endothelium upon contact with the luminal surface, and is tissue specific. One of ordinary skill in the art, given these teachings, would be able to identify similar such agents (e.g., antibodies). The actual antigen need not be identified, nor need the structure of the antigen be described, provided that the antibody have the relevant characteristic (binding to a component of caveolae of the luminal surface of the vascular endothelium, in a tissue-specific manner). Given the screening techniques described in the Specification, one of ordinary skill in the art would be able to determine whether an antigen had the relevant characteristic of binding to a component of caveolae of the luminal surface of the vascular endothelium, in a tissue-specific manner. For example, one of ordinary skill in the art

could use the methods described in the Examples to determine whether the antigen identified by the antibody is concentrated in caveolae similar to caveolin-1, but unlike the lipid raft marker, 5'nucleotidase (5'NT), using subfractionation of relevant tissue samples. Furthermore, the Specification provides ample detail regarding conjugation of various agents to the antibody and delivery of the agents in a tissue-specific manner. One of ordinary skill in the art, given these teachings, would be able to select an appropriate agent to be delivered in a tissue-specific manner. There are multiple tissues that can be targeted in the manner described in the Specification, including normal organs, different tissue compartments in organs, as well as diseased tissues, including tumors. The methods of the invention, as exemplified by the targeting of lung using Mab 833, demonstrates proof of concept that tissue specific targeting can be achieved *in vivo*.

CONCLUSION

In view of these considerations, the claims are in condition for allowance. Applicant's Attorney requests that all objections and rejections be reconsidered and withdrawn.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to call Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to call Doreen M. Hogle at (978) 341-0036.

Respectfully submitted,

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